IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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In re Application of:	:	
Pieczenik	:	Group Art Unit: 1805
Serial No. 07/662,764	:	Examiner: R. Lebovitz
Filed: February 28, 1991	:	
For: METHOD AND MEANS FOR SORTING AND IDENTIFYING BIOLOGICAL INFORMATION	:	

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May 15, 1992
(Date of deposit)

Lea Reavens
Name of Applicant, Assignee or Registered Representative

Lea Reavens
Signature

5/15/92
Date of signature

AMENDMENT

Hon. Commissioner of Patents
and Trademarks
Washington, D.C. 20231

Sir:

In response to the Office Action dated November 15, 1991, Applicants respectfully request reconsideration and reexamination. This amendment is accompanied by a Petition for Extension of Time. Please amend the application as follows:

In the Specification

At page 1, line 25, please insert a comma after "application" and insert --now abandoned,-- between "application," and "is".

At page 9, line 2, please insert --the-- between "of" and "discrete".

At page 28, line 24, please rewrite "gt11" as --λgt11--.

At page 40, line 13, please rewrite "a garose" as --agarose--

At page 48, line 9, please rewrite "endoplasmic" as --endoplasmin--.

In the Claims

Claim 1. (Once amended) A discrete population of oligonucleotides of random sequence wherein:

each member of the population comprises [between 1 and about 50 tandem sequences] a sequence of a selected length of from about 4 to about 12 nucleotide triplets, the order and ~~selection~~ identity of said triplets being random,

each of the [tandem] sequences encodes a corresponding peptide sequence of one of from about 4 to about 12 L-amino acid residues, and

wherein the sum of said corresponding peptide sequences represents at least about 10% of all possible corresponding peptide sequences of the selected length.

Please cancel claim 2 without prejudice as redundant over amended claim 1.

In claim 3, line 2, please delete "a single" and insert --said selected length-- therefor.

Claim 4. (Once amended) The oligonucleotide population of claim 1 wherein the population is generated by shearing of mammalian genetic material[.] and size fractionation.

Claim 6. (Once amended) A ~~discrete~~ population of recombinant vectors comprising:

substantially identical autonomously replicating nucleic acid sequences [wherein at least a portion of each nucleic acid sequence is a structural gene] which nucleic acid sequences comprise a structural gene into which insertions of nucleic acid sequences can be made, and

oligonucleotide inserts consisting essentially of a population of oligonucleotide inserts wherein each insert consists essentially of [one of from 1 to about 50 tandem sequences, each of] a sequence of [which is] from about 4 to about 12 nucleotide triplets, the order and identity ~~selection~~ of said triplets being random, and wherein each oligonucleotide insert has the

same [number of tandem sequences, and each sequence has the same] length, and

wherein each member of the population of oligonucleotides inserts is ~~recombinantly~~ inserted in vitro into the structural gene of the replicating sequences to form a recombinant structural gene, and

wherein [a significant portion of the] said recombinant vectors [is] are capable of expressing the recombinant structural gene when transferred into ~~appropriate~~ Escherichia coli host cells, and wherein expression of the recombinant structural genes yields polypeptides, each comprising a corresponding peptide sequence encoded by the oligonucleotide insert and each comprising one length of [from about 1 to about 50 tandem peptide sequences, each of] from about 4 to about 12 L-amino acid residues encoded by the respective oligonucleotide inserts.

Please cancel claim 7 without prejudice as redundant over amended claim 6.

Claim 19. (Once amended) The ~~discrete~~ oligonucleotide population of claim 1 wherein each of ~~said~~ encoded corresponding peptide sequences is capable of forming a binding pair with an antibody that has not been selected by immunization with said

peptide sequence or said peptide sequence in conjugated form, said antibody being selected from the group consisting of all antibodies produced by lymphoid-derived antibody-producing cells, where the group of all antibodies together is capable of binding to substantially all members of the discrete oligopeptide population encoded by the oligonucleotide population of claim 1.

Claim 20. (Once amended) The vector population of claim [1] 6 wherein each of the generated polypeptides is capable of forming a binding pair with an antibody that has not been elicited by immunization with said peptide or said peptide in conjugated form, said antibody being selected from the group consisting of all antibodies produced by lymphoid-derived antibody-producing cells, where the group of all antibodies together recognizes substantially all epitopic sequences.

Claim 21. (Once amended) A method of producing ~~a discrete~~ population of random epitopic peptide sequences in Escherichia coli, wherein said epitopic [seqeunces] sequences are each accessible to antibody recognition, comprising the steps of:

inserting in vitro oligonucleotides of random amino acid coding sequence [of] into a population of vector nucleic acid molecules within a structural gene to produce a recombinant vector such that said oligonucleotides express random epitopic

peptide sequences in a position where said epitopic peptide sequences are accessible to antibody recognition

whereby said discrete population of random epitopic peptide sequences comprises substantially every epitopic peptide sequence.

In claim 22, line 5, of the please rewrite "witha" as -- with a--.

REMARKS

Claims 1, 3-6 and 8-28 are pending in this case; claims 9-10 and 22-28 are withdrawn from consideration. Claims 2 and 7 have been canceled without prejudice as redundant over amended claims 1 and 6, respectively.

The Specification and claim 22 have been amended to correct several obvious typographical errors. Claims 1, 4, 6 and 19-21 have been amended to better claim the invention. Claims 2 and 7 have been cancelled without prejudice as redundant over amended claims 1 and 6. The language of amended claim 4 reciting size fractionation is supported by the Specification at page 19, line 19, and at page 27, lines 36-27. The amendment of claim 19 is supported by the Specification at page 8-9, bridging paragraph. Claim 20 has been amended to correctly recite dependency. None of

the amendments presented herein represent the addition of new matter.

The Restriction Requirement

The Examiner has required restriction of the claims. Applicants respectfully traverse this rejection.

Applicant confirms the provisional election of claims 1-8 and 11-21, made in a personal interview with the Examiner in October of 1991; however, that election was made with traverse. Correction of the record is respectfully requested.

It has been alleged that claims 1-8, drawn to oligonucleotide sequences, vectors containing them and methods of using them to produce peptides (Invention I), claims 9-10, drawn to peptides (Invention II), claims 22-24, drawn to method of producing a population of antibodies/hybridomas (Invention III), and claims 25-28, drawn to binding pairs comprising antibodies and cognate peptides (Invention IV), are distinct inventions.

While the inventions of groups I and II are related as process of making and product made, the oligonucleotides and peptides are so closely related by virtue of the fact that they represent coding sequences and sequences encoded, that it is respectfully requested that they be examined concurrently. The invention of Group III is

closely related to the invention of Group II in that the antibodies of Group III reacts with the peptides of Group II, which are encoded by the oligonucleotides of Group III. The Invention of Group IV combines the antibodies related to the Invention of Group III and the peptides of Group II. Thus, the inventions allegedly distinct are so closely intertwined that Applicant respectfully requests that all the claims in the instant case be examined as a whole.

The Rejections under 35 U.S.C. 112, first paragraph

The Specification has been objected to and claims 1-28 were rejected under 35 U.S.C. 112, first paragraph, with the Office Action alleging that the disclosure fails to provide an adequate written description of the invention and fails to provide an enabling disclosure. Applicant respectfully traverses this rejection.

The Examiner has acknowledged that a random oligonucleotide population is enabled, but has alleged that Applicants have failed to describe the expression of the random oligonucleotide population to form polypeptides. Applicants point out that it is inherent that insertion of coding nucleotides within a gene will result in translation of those coding oligonucleotides into protein, i.e. with the production of a fusion protein. Example IV demonstrates the insertion of coding nucleotides into the gene III of

bacteriophage f1; gene III encodes pIII, a minor coat protein. It naturally follows that the inserted coding sequences will be expressed and presented to the desired antibody on the surface of the bacteriophage particle. It is a mischaracterization of the disclosure to allege that Example IV "merely enables the construction of a random peptide DNA library." As exemplified, the random coding oligonucleotides are inserted within the gene encoding pIII -- there has been no sound scientific reasoning or evidence presented that these coding oligonucleotides will not be translated as if they were a natural part of the pIII coding sequence. Thus, it is believed that the disclosure does support the expression of the random oligonucleotide population as peptide sequences of random amino acid sequence, e.g. within a vector-encoded polypeptide.

The Office has alleged that Applicant has not demonstrated the operability of the invention and that there is "insufficient predictability that any peptide sequence could be expressed in a host and made accessible to antibody." He has noted possible sources of unpredictability: foreign peptides may be unstable, tandem or duplicative DNA structures may form secondary structures which are unstable or untranslatable, repeated proteins may form aggregates, small peptides are soluble and may be lost during the binding step. The Examiner has further alleged that no examples were disclosed in which random DNA sequences were expressed in the

claimed manner and that there is no disclosure as to whether intracellular or cell surface expression is preferable.

As a first matter, Applicant has indicated that expression of the peptide sequences on the surface of the host cell or bacteriophage is preferable. See, e,g, pages 17-18, bridging paragraph, which states:

> The nucleotide sequence is advantageously inserted in such a way that the peptide sequence encodes by the nucleotide sequence is expressed on the outside surface of the bacteriophage or the host cells...

The Examiner has presented a number of speculative sources of unpredictability in expression of the random oligonucleotide population, but there is nothing concrete cited to support a conclusion that the invention would not be operable. Therefore, the burden for doubting Applicant's broad enabling statements established by In re Marzocchi, 169 U.S.P.Q. (C.C.P.A. 1971) has not been met and the rejection has not been made proper.

While the specification does not present specific exemplification of the expression of a random oligonucleotide population and the detection of a particular epitope, Example V presents the successful demonstration of the insertion of a particular oligonucleotide sequence encoding an epitope of endoplasmin, its expression within the pIII protein of bacteriophage f1 and detection with antibody specific for the

cognate peptide epitope. There is no sound scientific reasoning on the record as to why any other oligonucleotide coding sequence could not be similarly expressed. In the Declaration of George Pieczenik, submitted herewith as Exhibit E with Figures 1-3, the specific binding of an endoplasmin epitope-specific antibody to a recombinant f1 bacteriophage expressing the cognate endoplasmin epitopic sequence is shown. As stated in the Pieczenik Declaration, this work was done prior to August of 1990, and was disclosed in the United States to others who understood the significance of those results. Those others included Roy Durham, as stated in the Declarations of Pieczenik (Exhibit E)*, of Lorance Greenlee (Exhibit A) and of Roy Durham (Exhibit D)* and as evidenced by the Pieczenik manuscript (Exhibit B), which was communicated to Durham and Greenlee in the United States before August 1990. Moreover, the Devlin, Scott and Smith and Cwirla et al. references all show the recovery of particular epitopes from similar populations of bacteriophage expressing random oligonucleotide sequences.

The Specification has been objected to and claims 6-18 were rejected for alleged failure of the Specification to provide and adequate written description and an enabling disclosure. Applicant respectfully traverses this rejection.

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*The executed Pieczenik and Durham Declarations are not yet available; therefore, the unsigned declarations are submitted herewith. The executed declarations will be promptly submitted to the Patent Office upon receipt by the undersigned.

It has been alleged that the Specification does not disclose information required to use any possible host cell, transformation protocols, vectors, suitable cell lines and selectable markers for host cells. It has been further alleged that "the expression of any peptide sequence by any host cell line could not be predicted." Possible mRNA secondary structure and the possible action of host cell proteases were raised as sources of unpredictability.

No support has been put forward in support of the speculative sources of unpredictability listed in the Office Action. In the absence of supporting scientific reasoning or evidence, as required by In re Marzocchi, supra, the rejection has not been made proper and should be withdrawn. In any event, the art knows many suitable cell lines, vectors and selectable markers for use in the expressing oligonucleotide coding sequence populations as disclosed in the present application. A patent need not teach and preferably omits what is well known to the art, according to Hybritech, Inc. v. Monoclonal Antibodies, Inc., 231 U.S.P.Q. 81, C.A.F.C., 1986).

With respect to the questioning of the operability of additional or other embodiments of the invention, an applicant is not required to demonstrate all possible embodiments of his invention.

In view of the foregoing arguments, the withdrawal of the rejections and objections under 35 U.S.C. 112, first paragraph, is respectfully requested.

The Rejection under 35 U.S.C. 112, second paragraph

The Examiner has rejected claims 1-8 and 11-21, alleging that they are indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Applicant respectfully traverses this rejection.

Claims 1 and 6 were alleged to be vague in the recitation of "between 1 and 50 tandem nucleotide sequences" and "each of the tandem sequences." Claims 1 and 6 were amended to delete reference to tandem sequences in order to more particularly point and more distinctly claim the subject matter of the invention. In view of the language of amended claims 1 and 6, it is believed that this aspect of the rejection is overcome.

The Examiner has further alleged that the recitation of it is unclear what number of sequences would correspond to 10% of all possible corresponding sequences." Applicant respectfully traverses this ground of rejection.

For a peptide of a selected length, the ordinary skilled artisan knows how to calculate the number of possible sequences.

For a peptide 5 amino acids in length, the are 5^{20}, or 3.2×10^6, possible peptide sequences. 10% of all possible sequences 5 amino acids in length is 3.2×10^5. The calculations for peptides of other selected lengths are carried out in a similar fashion. See, e.g., the Specification at Example IV. Thus, this recitation is not unclear. The ordinary skilled artisan understands what is meant, it is neither necessary nor meaningful nor practical to recite individual sequences.

The Examiner has questioned why 10% was chosen. A peptide population of a minimum of 10% of all possible peptide sequences was selected because of the degeneracy of the antibody-epitope recognition process. The specification at page 6, lines 6-12, notes that "linear sequences which differ in only one amino acid [from a particular epitope sequence] can compete for antibody binding with varying degrees of specificity." Geysen et al. (1986) in Synthetic Peptides as Antigens; Ciba Foundation Symposium 119, R. Porter and J. Wheelan, eds. (New York, Wiley), pp 130-149 develops this concept further. Thus, it follows that one does not need to have the complete universe of epitopic sequences in order to have a set of epitopic sequences which will be recognized by the universe of antibody binding sites. In fact it is one of the inventor's insights that the redundancy of epitopic configurations can be exploited in combination with all other aspects of the invention to reduce to a manageable size the number of random sequences to be screened.

Claims 2, 3, 7 and 8 were alleged to be vague and indefinite because it was alleged to be unclear what is intended to be claimed. It is believed that this ground of rejection is made moot by the amendment of claims 1 and 6 to remove language related to tandem sequences.

Claim 4 was alleged to be vague and indefinite for failing to set forth all the steps of the claim process. The Examiner has noted that there is no process step by which the sheared DNA is converted in to a population of oligonucleotides having the claimed characteristics. It is believed that the amendment of claim 4 to include a step of size fractionation overcomes this ground of rejection. This amendment is supported in the Specification at page 27, lines 36-37, and at page 19, line 19.

Claim 6 is allegedly rendered vague by the language "wherein at least a portion ... is a structural gene" because the extent of the gene is not limited by size or function. This aspect of the rejection is believed to be overcome by the amended language of claim 6 which states that the vector comprises a structural gene into which the coding oligonucleotides can be inserted.

Claim 6 was further alleged to be vague in the recitation of "recombinantly inserted" and in the recitation of "significant portion." Claim 6 was amended by the insertion of the phrase "in

vitro" after "recombinantly inserted." It is believed that this amended language makes clear how the sequences were inserted. This amendment is supported by the disclosure of the Examples. The language " wherein a significant portion of the vectors is capable of expressing..." has been amended to recite "wherein said recombinant vectors are capable of expressing..." It is believed that these amendments to claim 6 are responsive to this ground of rejection.

Claims 19 and 20 were alleged to be vague in the recitation of "all antibodies produced by the lymphoid-derived antibody producing cells," because one of ordinary skill would be unable to determine the metes and bounds of the invention. Claims 19 and 20 have been amended to recite that the population of antibodies comprises antibodies capable of binding to substantially all members of the discrete oligopeptide population encoded by the oligonucleotide population of claim 1. This amendment is supported by the Specification at page 9-10, bridging paragraph.

Claim 21 is allegedly incomplete for failing to recite all the process steps in which a peptide is made "accessible to antibody recognition." This objection is not understood in view of the fact that the method claim is of "producing a discrete population of random epitopic peptide sequences." The Specification, in the paragraph bridging pages 17-18, states that the peptide coding sequences are advantageously inserted into a protein such that the

epitope is expressed on the surface of the host cell or bacteriophage. In those cases, no step is necessary -- access to antibody recognition is inherent. The claim language states that the oligonucleotides are inserted into a structural gene of the vector such that the epitopic sequences encoded by the oligonucleotides are accessible to antibody recognition. No step is required to make those epitopic sequences accessible -- the insertion site within the structural gene confers accessibility. The art knows (and knew as of filing date) how to locate accessible positions. It is believed that no amendment of the claim is necessary, and the withdrawal of this aspect of the rejection under 35 U.S.C. 112, second paragraph, is respectfully requested.

In view of the amendments to the claims and the foregoing arguments, Applicant respectfully requests the withdrawal of this rejection.

The Rejection under 35 U.S.C.102

Claims 1-3, 5-8, 11-15 and 17-21 were rejected under 35 U.S.C. 102 (a or b) as allegedly anticipated by any one of Wells et al. (1985), Ballivet et al. (1987), Parmley et al. (1988), Devlin et al. (1990), Scott et al. (1990) or Cwirla et al. (1990). Applicant respectfully traverses this rejection.

The Examiner has alleged that the enablement for making the random oligonucleotide library was not accomplished until the filing of the present application, i.e. it has been alleged that the present application is not entitled to the filing date of the ultimate parent application, USSN 770,390, filed August 28, 1985. Applicants respectfully traverse this statement.

While the present application presents additional disclosure and specific examples, the oligonucleotide population of the invention was enabled by the ultimate priority application, taken together with what was known to the art as of the filing date of said ultimate parent (August 28, 1985). The parental application teaches the use of oligonucleotides of random sequence. Examples I and II teach the isolation of a population of oligonucleotides of random sequence and of a selected length prepared by mechanical shearing of mammalian cDNA, e.g., from bovine pancreas. The present application adds an example demonstrating the insertion of random oligonucleotides generated by chemical synthesis into a minor coat protein (pIII) gene of bacteriophage f1. The reactivity of a model f1 recombinant expressing an endoplasmin epitope with cognate antibody is also disclosed in the present application, and the accompanying Declaration of George Pieczenik (Exhibit E). The material not originally disclosed is not required for the enablement of the invention as claimed.

The filing of the instant Continuation-in-Part Application does not, and should not be taken to, constitute an acquiescence of any of the rejections made in the applications from which priority is claimed. Paperless Accounting, Inc. v. Bay Area Rapid Transit Sys., 231 U.S.P.Q. 649, 652 (C.A.F.C. 1986), cert. denied, 480 U.S. 933 (1987) states

> The filing of a continuation-in-part, in and of itself, is not an admission of the correctness of a rejection., Law and policy liberally authorize the filing of c-i-p applications for a number of reasons, whether to enlarge the disclosure to include new technological information, thereby providing the public with knowledge of recent developments or improvements; or to enable more extensive prosecution or improved draftsmanship of specification or claims; or to provide a vehicle for prosecution of nonelected claims.
>
> ...the mere filing of a continuation-in-part with additional matter or revised claims is not of itself an admission that the matter is 'new' or that the original application was legally insufficient to support the claims.

Thus, Applicant is entitled to the filing date of the grandparental application, which predates the cited references. Applicant has stated in the record, during the prosecution of those applications and in the Letter of Express Abandonment of February 28, 1991, that he did not acquiesce to any of the outstanding rejections.

Even if all the claims of the instant application were not deemed to be entitled to the August 28, 1985 filing date, Applicant submits showings herewith that a bacteriophage library of random-sequence oligonucleotide inserts was made and the capacity for

screening a bacteriophage recombinant expressing a particular epitope with a cognate antibody was carried out before the publication of the Cwirla, Devlin and Scott references. The appended Declarations of Lorance Greenlee (Exhibit A), Roy Durham (Exhibit D) and George Pieczenik (Exhibit E, with supporting Figures 1-3), and the supporting documents (Exhibits B and C) shows that this invention was made before the Cwirla et al., Scott et al. and Devlin et al. references were published in 1990. Accordingly, the withdrawal of these references as prior art against this application is respectfully requested.

The Ballivet reference is alleged to teach pools of random oligonucleotides which encode peptides. Recombinant genes formed by joining shorter oligonucleotides in tandem are to be screened by a variety of methods, including by antibodies.

The Ballivet reference was published in June 1987, a date after the filing date of the grandparental application of the instant application. Accordingly, this application is not properly cited as prior art against this case.

At page 1, second paragraph, Ballivet refers to "stochastic genes or fragments of stochastic genes" capable of producing "completely new proteins." In the instant case are oligonucleotides containing random sequence of from 12-36 nucleotides. In the vectors comprising these sequences, there re

expressed proteins which are mostly a vector protein in which there is an insertion of a small amino acid sequence -- of from to 12 amino acids. Therefore, this is not a "completely new" protein, but rather a mostly old protein. At page 3, Ballivet teaches the synthesis of polynucleotides of some 300 bases -- sequences containing roughly 10 times the length of the claimed coding oligonucleotides of random sequence, which are about 12 to about 36 bases in length. At page 4, bottom of column 1, there is reference to ligating together 20-100 oligomers, where the oligomers are 8 bases pairs in length -- again, significantly longer polynucleotides than those claimed in the present application. At pages 2, 4 and others, Ballivet refers to the use of palindromic nucleotides; by definition, palindromic sequences are not random. In view of the differences between the stochastic polynucleotides and vectors containing them of Ballivet and the instant claimed random coding oligonucleotides and vectors containing them, it is respectfully submitted that the Ballivet reference does not anticipate the instant claimed invention.

The Parmley reference is said to teach an epitope library of short random coding sequences of about 6 amino acids in length to be analyzed by antibody binding to host cells. The statements at page 316 related to the epitope library suggest the creation of an epitope library and describe it in terms of the number of sequences to be incorporated into the vector. These statements do not go beyond the disclosure of grandparental application USSN 06/770,390

(filed August 28, 1985), and therefore do not constitute an anticipation of the claims of the instant application.

In view of the foregoing arguments in which Applicant has distinguished his invention over the disclosure in the cited references, the withdrawal of this rejection under 35 U.S.C. 102 (a or b) is respectfully requested .

Claims 1-4, 6-8, 10-15, and 19-21 were rejected under 35 USC 102 (a or b) for alleged anticipation by Robbins et al. (1984), Nunberg et al. (1984), Dame et al. (1984) and Mocarski et al. (1985). Applicant respectfully traverses this rejection.

It has been alleged that each of the cited references teach the construction of random epitope libraries and expressing them to identify the DNA encoding the epitope. The invention as claimed relates to random coding sequences. The Nunberg, Dame and Nunberg references each disclose the insertion of a set of oligonucleotides which are derived from a specific source; i.e., for Robbins the source is PRV genomic DNA, for Nunberg the source is the GA-FeLV envelope gene and for Dame the source is the sequence encoding a Plasmodium surface antigen. In view of the defined sources of the oligonucleotides, the population of oligonucleotides will not be random in sequence. Thus, these references do not anticipate the invention as claimed in the present application.

Mocarski et al. teaches the insertion of random fragments of the cytomegalovirus (CMV) genome in the expression vector lambda gt11 and screening for the production of polypeptides cross-reacting with monoclonal antibodies specific for specific viral proteins. The coding inserts of the present invention are distinguished from those of the Mocarski reference in that those of Mocarski were 400-500 bp on average; those of the present invention were 12-36 bp in length. Moreover, the inserted sequences in the Mocarski expression library were not random in view of the relatively large size of the inserts and the single genomic source of the DNA.

The Robbins abstract, as provided, discloses the cloning of 500 bp fragments derived from the pseudorabies virus (PRV) genome and the subsequent screening with antibody specific for the PRV glycoprotein. The Robbins inserts were larger (ca. 500 bp) than the coding oligonucleotides as claimed in the present application (12-36 bp). Furthermore, the Robbins nucleotides were not random in sequence because they were relatively large fragments derived from a source DNA of particular sequence.

The Wells reference teaches cassette mutagenesis using oligonucleotides, for example to introduce a desired restriction site into a target site. The summary states in part,

> The restriction sites to be introduced are chosen based on their uniqueness to the plasmids, proximity to the

target codon and conservation of the final amino acid coding sequence.

The technique was applied to substitution at a particular methionine residue labile to oxidation in the protease subtilisin. While all 19 alternative amino acids were tested in place of the methionine, the oligonucleotides inserted were not random in sequence, and random epitopic amino acid sequences were not produced, only sequences in regions including methionine residues were varied by substitution of an alternate amino acid for the methionine.

In view of the foregoing showings and the appended declaration of Inventor Pieczenik, the withdrawal of the rejections under 35 USC 102 (a or b) is respectfully withdrawn.

The Rejection under 35 U.S.C. 103

Claims 1-8 and 11-21 have been rejected under 35 U.S.C.103, for alleged unpatentability over Wells et al. or Ballivet et al. in view of Dame et al. Applicant respectfully traverses this rejection.

The Wells reference is alleged to teach a pool of random oligonucleotides encoding about 8 amino acids which are used to create random mutations in proteins. The oligonucleotides are inserted into a protein and expressed by host cells. There is no

teaching or showing that the mutations so created are to be used to study epitopes exogenous to said protein, but rather these mutations are said to be used to study regions of said protein important for functionality of said protein. The Ballivet reference is alleged to teach pools of random oligonucleotides which encode peptides.

It has been noted that neither the Wells nor the Ballivet references teach the construction and expression of proteins encoded by random sequences, and they do not teach the expression of tandem sequences. Dame et al. teaches the immunogenicity of tandem sequences, and it has been alleged that the ordinary skilled artisan would have combined the concepts to express tandem random sequences. Further more. the Ballivet reference appears to have been published in June of 1987, a date after the filing of the ultimate parent of the present application.

As stated in the arguments presented in response to the rejection under 35 USC 102, neither the Ballivet nor the Wells reference actually teaches the expression of <u>random</u> sequences.

The Wells reference teaches cassette mutagenesis using oligonucleotides, for example to introduce a desired restriction site into a target site. The summary states in part,

> The restriction sites to be introduced are chosen based on their uniqueness to the plasmids, proximity to the

target codon and conservation of the final amino acid coding sequence.

The technique was applied to substitution at a particular methionine residue labile to oxidation in the protease subtilisin. While all 19 alternative amino acids were tested in place of the methionine, the oligonucleotides inserted were not random in sequence, and random epitopic amino acid sequences were not produced.

Applicant notes that the Ballivet reference was published after the filing date of the application from which priority is ultimately claimed in this case. Accordingly, it is not properly cited as prior art against the instant application, which claims priority from grandparental application USSN 06/770,390, filed August 28, 1985.

In view of the above arguments, Applicant maintain that the Examiner has not made a prima facie case for obviousness over the cited references. Accordingly, the withdrawal of this rejection is respectfully requested.

Conclusion

In view of the foregoing amendments and arguments, it is submitted that this application is in condition for allowance and passage to issuance is respectfully requested.

Should the Examiner wish to maintain any of the rejections discussed above, a telephone interview is respectfully requested, and the Examiner is invited to telephone the undersigned to arrange a mutually convenient time.

This amendment is accompanied by a Petition for Extension of Time (three months) and a check in the amount of $405 for the extension fee under 37 C.F.R. 1.17 (c). It is believed that the present amendment does not necessitate the payment of any additional fees. If this is incorrect, please deduct any deficiency or credit any overpayment to deposit account No. 07-1969.

Respectfully submitted,

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leb: May 15, 1992